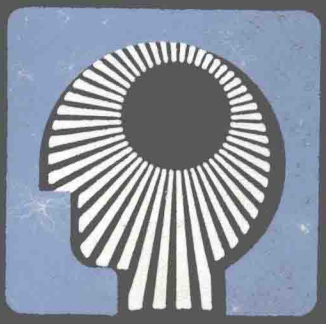
CNS Complications of Malignant Disease

Edited by
J.M.A. Whitehouse
and H.E.M. Kay



CNS COMPLICATIONS OF MALIGNANT DISEASE

Edited by

J. M. A. WHITEHOUSE

Director of the CRC Medical Oncology Unit, Southampton General Hospital, United Kingdom

and

H. E. M. KAY

Consultant Haematologist, Royal Marsden Hospital, London

UNIVERSITY PARK PRESS
Baltimore

First published 1979 by
The Macmillan Press Ltd
London and Basingstoke

Published in North America by
UNIVERSITY PARK PRESS
233 East Redwood Street
Baltimore, Maryland 21202

ISBN: 0-8391-1494-X

Printed in Great Britain

British Library Cataloguing in Publication Data

CNS complications of malignant disease.
1. Central nervous system - Cancer - Congresses
I. Title II. Whitehouse, J M A
III. Kay, H E M
616.9'94'8 RC280.N43

LCCN: 79-67872

CNS COMPLICATIONS OF MALIGNANT DISEASE

Foreword

New developments in treatment have greatly influenced the ultimate course of many malignant tumours. Some of the most substantial improvements in prognosis have been in the acute leukaemias and in the lymphomas. The natural history of one of these conditions, namely acute lymphoblastic leukaemia, was so modified by chemotherapy that central nervous system infiltration, which previously had been only rarely recorded, became one of the commonest and most serious complications. As therapeutic interest has focused on this problem, so there has grown an awareness of the importance of the central nervous system (CNS) as a sanctuary site in this and other neoplasms. The very real difficulties of assessing and treating malignant disease in the CNS led to the organisation of an international symposium in 1978 in Southampton, England to collect the clinical and experimental data from scientists and clinical specialists of various disciplines.

The range of their experience reflects the complexities of the problems because although the many associations between malignant disease in its various forms and the CNS are well known, the contrasts between the characteristics of the two cell systems are conspicuous. The behaviour of most proliferating tumour cells which grow and spread, often via lymphatics, is utterly unlike the normal physiology of the CNS where cell turnover is minimal, where there is no lymphatic system and where the whole tissue is uniquely protected by the blood-brain barrier. Tumours can of course arise from any of the cells which comprise the CNS and metastases blood-borne from outside the CNS are common. The former are peculiar in their limited capacity for metastasis but all tumours in the CNS present special difficulties in diagnosis and, because of the blood-brain barrier, in their treatment by cytotoxic drugs.

Many of the problems are epitomised in the diagnosis and treatment of acute lymphoblastic leukaemia (ALL). This is exemplified in Section One, where Dr Price describes the process of meningeal infiltration and two pathological entities attributable to therapy.

This leads to a general consideration of strategy in the prophylaxis and treatment of leukaemia in the CNS in Section Two. (Purists may wish to refer to early pre-symptomatic treatment rather than prophylaxis or prevention.) The benefits of radiation and of methotrexate are limited by their damaging side effects, some of which are considered in detail in Section Six, so that the alternatives propounded by Drs Simone, Clarkson and Sinks need careful comparison. One point which requires emphasis is the long-term effects of these relatively recent treatments, especially the possibility of second tumour formation which can as yet only be surmised but must probably be counted as a debit against radiation-dependent regimens.

The problem of CNS infiltration in acute myelogenous leukaemia (AML) and in blast crisis of chronic myeloid leukaemia is considered but obviously remains of minor importance until better general control of systemic disease can be achieved. In Section Three the incidence of lymphomatous infiltration is assessed. Here again, the value of treatment directed at the CNS is at present small, but must be enhanced if and when more effective general treatment is developed. Section Four outlines a single but important complication of myeloma and indicates the value of energetic treatment of paraplegia in these patients.

Section Five deals with an all too familiar problem, that of cranial metastases from bronchial carcinoma. As with lymphoma the results of trials show that some benefits can be gained from prophylaxis but the major problem still lies outside the CNS.

Sections Six and Seven deal with some of the complications of therapy and show that the margin of safety is narrow. The negative CAT scan data from Bristol will be reassuring and lend some support to the concept that such abnormalities occur only when radiation is combined with relatively large cumulative doses of methotrexate. It is also reassuring that current regimens appear to cause insignificant damage to the hypothalamus and pituitary function but the impairment of intellectual function, documented by Dr Eiser, must be taken as a warning of the need to modify current regimens. The hazard of activating neuroviruses through immunosuppressive treatments is also real, but specific antiviral chemotherapy is now becoming available. In this section also, Dr Webb's wide-ranging review of the role of neuroviruses in relation to malignant disease is a reminder of the scope of possible progress. Section Eight outlines some new approaches to diagnostic technology and defines existing limitations in diagnosis, while Section Nine summarises the scope of surgery and radiotherapy, presenting a detailed review of achievements attributable to radiotherapy and also an indication of the limitations of this technique. Improvements must lie with the possible use of radiation potentiators or as described in Section Ten with new agents, new techniques of administration and a much greater understanding of the pharmacokinetics and interactions of currently available drugs.

None of the discussions has been reproduced in the book, but many of the authors have adapted their texts to cover some of the points which were raised. Although no clear pattern of investigation or management has yet emerged it is to be hoped that the current strong interest in neoplastic infiltration of the CNS demonstrated in this book will provoke additional study and this, in turn, further improvements in prognosis.

Southampton University Hospitals, Southampton J.M.A.W.
Royal Marsden Hospital, London H.E.M.K.

Symposium Contributors

Dr H. T. Abelson
Sidney Farber Cancer Center,
Boston, Massachusetts 02115,
USA

Dr T. Anderson,
Medicine Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr Z. A. Arlin,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr D. Ash,
Regional Radiotherapy Centre,
Cookridge Hospital,
Leeds

Dr Rhomes J. A. Aur,
Stanford Children's Hospital,
California, USA

Professor K. D. Bagshawe
Department of Medical Oncology,
Charing Cross Hospital,
Fulham Palace Road,
London W6 8RF

Dr C. G. Beardwell,
Department of Endocrinology,
Christie Hospital and Holt Radium Institute,
Manchester

Dr W. Bleyer,
Pediatric Oncology Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr H. J. G. Bloom,
Department of Radiotherapy,
Royal Marsden Hospital,
London

Dr R. L. Brearley,
Department of Haematology,
St Bartholomew's Hospital,
London

Dr P. Brodersen,
Finsen Institute,
Copenhagen,
Denmark

Dr L. Brown,
Haematology Department,
St Bartholomew's Hospital,
London

Dr J. Bullimore,
Department of Child Assessment,
Royal Hospital for Sick Children,
Bristol

Dr J. H. Burchenal,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr E. H. Burrows,
Wessex Neurological Centre,
Southampton General Hospital,
Southampton

Dr George P. Canellos,
Division of Medicine,
Sidney Farber Cancer Center,
Boston, Massachusetts 02115, USA

Dr Bruce Chabner,
Clinical Pharmacology Branch,
Division of Cancer Treatment,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr Bayard D. Clarkson,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr H. M. Clink,
Royal Marsden Hospital,
Sutton, Surrey

Dr L. Cohen,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Professor D. Crowther,
Department of Medical Oncology,
Christie Hospital and Holt Radium Institute,
Manchester

Dr M. H. Cullen,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr R. Dalton
Department of Child Assessment,
Royal Hospital for Sick Children,
Bristol

Dr R. E. Day,
Assessment Unit,
Royal Hospital for Sick Children,
Glasgow

Dr V. T. DeVita,
Medicine Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr M. D. Dowling,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr J. Drake,
Clinical Pharmacology Branch,
Division of Cancer Treatment,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr J. Driscoll,
Clinical Pharmacology Branch,
Division of Cancer Treatment,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr P. DuFour,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr J. Durrant,
Horton General Hospital,
Banbury

Dr C. Eiser,
Department of Psychology,
The Hospital for Sick Children,
Great Ormond Street,
London

Dr W. Ensminger,
Pediatric Oncology Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr T. Ervin,
Division of Medicine,
Sidney Farber Cancer Center,
Boston, Massachusetts 02115, USA

Dr Arnold I. Freeman,
Vincent T. Lombardi Cancer Research Center,
Georgetown University Medical Center,
Washington D. C. 20007, USA

Dr J. E. Freeman,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr Emil J. Freireich,
M.D. Anderson Hospital and Tumour Institute
Texas Medical Center,
Houston, Texas 77025, USA

Dr J. Galicich,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr D. Gangji,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20205, USA

Dr H. Gaya,
Department of Bacteriology,
St Mary's Hospital,
London

Dr T. S. Gee,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr D. Glaubiger,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr J. Gouveia,
Institut De Cancerologie de D'Immunogenetique,
Groupe Hospitalier Paul Brousse,
Villejuif, France

Dr M. Haghbin,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr K. Hande,
Clinical Pharmacology Branch,
Division of Cancer Treatment,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr H. H. Hansen,
Finsen Institute,
Copenhagen,
Denmark

Dr F. Hirsch,
Finsen Institute,
Copenhagen,
Denmark

Dr D. M. Howser,
Medicine Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr H. Omar Hustu,
Stanford Children's Hospital,
California, USA

Dr E. Jaffe,
Medicine Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr S. Jagelman,
Department of Neurology,
St Thomas' Hospital,
London

Dr B. Jameson
Royal Marsden Hospital,
Sutton, Surrey

Dr G. Janossy,
Horton General Hospital,
Banbury

Professor C. Jasmin,
Institut De Cancerologie et D'Immunogenetique,
Groupe Hospitalier Paul Brousse,
Villejuif, France

Dr B. E. Juel-Jensen,
University of Oxford,
Radcliffe Infirmary,
Oxford

Dr H. E. M. Kay,
Department of Clinical Pathology,
Royal Marsden Hospital,
Fulham Road,
London

Dr S. Kaye,
Department of Medical Oncology,
Charing Cross Hospital,
London

Dr P. Kearney,
Department of Child Assessment,
Royal Hospital for Sick Children,
Bristol

Dr S. Kempin,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr J. Kingston,
Department of Child Assessment,
Royal Hospital for Sick Children,
Bristol

Dr N. Larnicol,
Institute De Cancerologie et D'Immunogenetique,
Groupe Hospitalier Paul Brousse,
Villejuif, France

Dr T. A. Lister,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr T. J. McElwain,
Royal Marsden Hospital,
Sutton, Surrey

Dr J. Malpas,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr G. Mathé,
Institut De Cancerologie et D'Immunogenetique,
Groupe Hospitalier Paul Brousse,
Villejuif, France

Dr J. L. Misset,
Institut De Cancerologie et D'Immunogenetique,
Groupe Hospitalier Paul Brousse,
Villejuif, France

Dr M. G. Mott,
Department of Child Assessment,
Royal Hospital for Sick Children,
Bristol

Dr M. L. Murphy,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr H. Nielsen,
Finsen Institute,
Copenhagen,
Denmark

Dr D. Parker,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr S. Passe,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr O. Paulson,
Finsen Institute,
Copenhagen,
Denmark

Dr A. M. Paxton,
Haematology Department,
St Bartholomew's Hospital,
London

Dr D. Poplack,
Pediatric Oncology Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr C. Portlock,
Division of Medical Oncology,
Stanford University Medical School,
California, USA

Dr J. Posner,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

Dr R. L. Powles,
Royal Marsden Hospital,
Sutton, Surrey

Dr R. A. Price,
St Jude Children's Research Hospital,
Memphis, Tennessee, USA

Dr J. K. H. Rees,
Department of Haematological Medicine,
University of Cambridge,
Cambridge

Dr A. Rosowsky,
Pediatric Oncology Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr R. Sandland,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr J. Scarffe,
Department of Medical Oncology,
Christie Hospital and Holt Radium Institute,
Manchester

Dr S. Shalet,
Department of Endocrinology,
Christie Hospital and Holt Radium Institute,
Manchester

Dr W. Shapiro,
Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, USA

M. Sharr,
Mersey Regional Department of
Medical and Surgical Neurology,
Walton Hospital,
Liverpool

Dr P. Sheaff,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr S. Shuster,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr J. V. Simone,
Stanford Children's Hospital,
California, USA

Dr Lucius F. Sinks,
Vincent T. Lombardi Cancer Research Center,
Georgetown University Medical Center,
Washington D.C. 20007, USA

Dr A. T. Skarin,
Division of Medicine,
Sidney Farber Cancer Center,
Boston, Massachusetts 02115, USA

Dr S. B. J. Sutcliffe,
Department of Medical Oncology,
St Bartholomew's Hospital,
London

Dr P. Swift,
Paediatric Department,
Royal Devon and Exeter Hospital,
Exeter

Dr J. Thomson,
Department of Child Assessment,
Royal Hospital for Sick Children,
Bristol

Dr J. Uren,
Pediatric Oncology Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr F. de Vassal,
Institut De Cancerologie et D'Immunogenetique,
Groupe Hospitalier Paul Brousse,
Villejuif, France

Dr J. Vraa-Jensen,
Finsen Institute,
Copenhagen,
Denmark

Dr Jaw J. Wang,
Vincent T. Lombardi Cancer Research Center,
Georgetown University Medical Center,
Washington D.C., USA

Dr J. Warwick,
Department of Medical Oncology,
Christie Hospital and Holt Radium Institute,
Manchester

Dr H. E. Webb,
Department of Neurology,
St Thomas' Hospital,
London

Dr H. Weinstein,
Division of Medicine.
Sidney Farber Cancer Center,
Boston, Massachusetts 02115, USA

Dr C. J. H. Williams,
Medical Oncology Unit,
Southampton General Hospital,
Southampton

Dr M. L. N. Willoughby,
Royal Hospital for Sick Children,
Glasgow, Scotland

Dr J. Wood,
Pediatric Oncology Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Dr R. K. Woodruff,
Horton General Hospital,
Banbury

Dr Robert C. Young,
Medicine Branch,
National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland 20014, USA

Acknowledgements

No new book of this kind can possibly be produced without the assistance of large numbers of people; however, the Editors would particularly like to thank the many contributors, the staff of the Wessex Regional Medical Oncology Unit, the Wessex Cancer Organisation and the organising committee including Mr Andrew Hayes, Dr Peter Bodkin, Professor Derek Crowther, Dr James Malpas, Dr Tim McElwain and Professor Michael Peckham, who helped to make the Symposium a success. Generous financial and organisational support was provided by Lederle Limited, to whom the Editors and the organising committee are indebted.

Contents

Section Ten: Pharmacological Aspects of Chemotherapy for Metabolic Disease of the CNS

Section One

HISTOPATHOGENESIS OF MENINGEAL LEUKAEMIA